PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P10975PC	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2004/000482	International filing date *(day/month/year)* 05.07.2004	Priority date *(day/month/year)* 04.07.2003
International Patent Classification (IPC) or national classification and IPC A61K9/28, A61K9/50, A61K38/29		
Applicant NYCOMED DANMARK ApS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.04.2005	01.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Epskamp, S Telephone No. +31 70 340-2857

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International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-65	as originally filed

Claims, Numbers

1-51	received on 08.11.2005 with letter of 08.11.2005

Drawings, Sheets

1/3-3/3	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 50 and 51 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 50 and 51 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	14,20-26,28-32,35,36,42-49,51
	No:	Claims	1-13,15-19,27,33,34,37-41,50
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-51
Industrial applicability (IA)	Yes:	Claims	1-49
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 8/11/05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

claim 1: The in vitro dissolution test is described by a combination of features which was not disclosed in the application as originally filed. The closest basis for this description of an in vitro test would be claims 1 and 2, in combination with page 32, lines 1-7, and claim 21. The preferred pH conditions (i.e. first 0.1 N HCl and then pH 6.8) and the duration of the first time period (two hours) could be derived from page 20, line 28 - page 22, line 33 and the examples. That 60% of the composition is to be released within 2 hours after the lag time has a basis in claim 25.

The following features from claim 21 and/or page 32, lines 1-7, have however been omitted: that the release has to be determined as an average of at least 3 (claim 21) or 6 (page 32) determinations, and that during the lag time not more than 10% of the active substance is to be released (both claim 21 and page 32). As no other basis for the amendments to claim 1 could be found (page 22, line 35 ff could also relate to in vivo release), these features should be present in claim 1.

All other amendments are considered to fulfill the requirements of Art 34(2)(b).

Note that claim 21 is now broader than claim 1.

Consequently, the present report will be based on the claims as originally filed. An opinion will however also be given on claim 1 as if it would have been amended as suggested above.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 50 and 51 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:
D1: EP 0 943 336 A
D2: EP 0 366 621 A
D3: WO 01/68058 A
D4: EP 0 225 189 A
D5: EP 0 621 032 A

Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-13, 15-19, 27, 33, 34, 37-41 and 50 is not new in the sense of Article 33(2) PCT.
Document D1 (§§ 9, 10 and 50; test examples 3 and 5, and powder composition 2; claims) discloses enteric-coated capsules comprising PTH (1-34) and a polyvalent metal carrier compound, e.g. a calcium compound such as calcium carbonate. As claim 1 merely appears to describe, in release characteristics, an enteric composition, no difference can be seen between claim 1 and D1.
Hence, claims 1-13, 15-19, 27, 33, 34, 37-41 and 50 are considered to lack novelty over D1. Claim 1 as filed 8/11/05, when correctly amended (see Item I), would have been considered novel over D1.
Claims 14, 20-26, 28-32, 35, 36, 42-49 and 51 appear to be novel.

Inventive Step

1 - Not being novel, claims 1-13, 15-19, 27, 33, 34, 37-41 and 50 cannot be considered inventive (Article 33(3) PCT).
2 - Independent claim 44 differs from D1 in that it specifies that the composition is to be used for the treatment or prevention of bone-related diseases (D1 is silent about the use of its PTH compositions).
As there is no synergistic effect demonstrated for the combined use of PTH and calcium, the problem to be solved can only be seen as to provide an alternative treatment.
This can however not be seen as inventive (Article 33(3) PCT), as the use of PTH and calcium for such diseases is generally known, see e.g. the prior art cited in the application, pages 6 and 7.
3 - Similar argument apply to independent claim 51, which thus also lacks an inventive step under Article 33(3) PCT.

4 - Dependent claims 14, 20-26, 28-32, 35, 36, 42, 43 and 45-49 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step with respect to the prior art named in the present proceedings. The reasons therefor are that the additional features of the said dependent claims (as far as clear) are a combination of features obvious to the skilled person in consideration of documents D1-D6 (see passages cited in the search report), or they concern minor modifications which lie within the normal practice of the skilled person.

5 - Claim 1 as filed 8/11/05, when correctly amended (see Item I), would not be considered inventive over D1.

Such a claim 1 would mainly appear to differ from the enteric-coated capsules of D1 in that the in vitro release profile has a lag time, which would result in the release of PTH being delayed after passing the stomach.

Delaying the release of an active in order to target a different part of the intestines is considered obvious for the person skilled in the art. Furthermore, D2-D5 disclose such compositions where the release of the active is delayed, listing PTH as possible active to be used (see search report for the relevant passages).

Industrial applicability

Claims 1-49 comply with the requirements of Article 33(4) PCT (see also Item III).

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CLAIMS as amended 8 November 2005 in response to Invitation pursuant to Rules 66.2 c), 66.3 and 66.4 of the PCT

1 (amended). A pharmaceutical composition for oral administration comprising PTH, wherein the *in vitro* release of PTH **is a combined pH controlled and a time controlled release such that – when tested in an in vitro dissolution test** of pharmacopoeia standard

i) for the first two hours employing 0.1 N HCl equilibrated at 37 °C as the dissolution medium – at the most about 10% w/w such as, e.g., at the most about 7.5% w/w, at the most about 5% w/w, at the most about 2.5% w/w, at the most about 1% w/w of PTH contained in the composition is released 2 hours after start of the test,

ii) followed by a change in the dissolution medium to pH 6.8 and a lag time of from about 0.5 to 8 hours, whereupon

iii) at least 60% of the PTH is released within a second time period of not more than 2 hours.

2. (new) A pharmaceutical composition according to claim 1, wherein the lag time is from 1 to 7 hours.

3. (new) A pharmaceutical composition according to claim 1, wherein at least 70% w/w such as, e.g., at least 75% w/w, at least 80%, at least 85% w/w, at least 90% w/w, at least 95% w/w or at least 99% w/w is released within the second time period of not more than about 2 hours.

4. (previous claim 3) A pharmaceutical composition according to any of claims 1-3 for delivery of PTH to the small intestine and/or to the colon.

5. (previous claim 4) A pharmaceutical composition according to any of the preceding claims for delivery of PTH to the jejunum.

6. A pharmaceutical composition according to any of claims 1-3 for delivery of PTH to ileum.

7. A pharmaceutical composition according to claim 6, wherein – when tested in an *in vitro* dissolution test employing a dissolution medium having a pH of about 6.8 and a temperature of about 37 °C – the following dissolution patterns of PTH are obtained (after start at pH 6.8):

at 2 hours 30 min	approx. 20% w/w (limits 0-50 % w/w)
at 3 hours 30 min	approx. 80% w/w (limits 25-100% w/w)
at 4 hours 30 min	approx. 100% w/w (limits 50-100% w/w).

8. A pharmaceutical composition according to any of claims 1-3 for delivery of PTH to colon.

9. A pharmaceutical composition according to claim 8, wherein – when tested in an *in vitro* dissolution test employing a dissolution medium having a pH of about 6.8 and a temperature of about 37 °C – the following dissolution patterns of PTH are obtained (after start at pH 6.8):

at 4 hours	approx. 20% w/w (limits 0-50 % w/w)
at 5 hours	approx. 80% w/w (limits 25-100% w/w)
at 6 hours	approx. 100 % w/w (limits 50-100% w/w).

10. A pharmaceutical composition according to any of the preceding claims, wherein PTH is recombinant or of mammalian origin including human and is selected from full-length PTH (1-84) or its amino terminal fragment, PTH (e.g. PTH 1-34 etc).

11. A pharmaceutical composition according to any of the preceding claims further comprising a calcium-containing compound.

12. A pharmaceutical composition according to claim 11, wherein – when tested in an in vitro dissolution test employing 0.1 N HCl equilibrated at 37 °C as the dissolution medium – the following dissolution pattern of calcium is obtained:

at 15 min.	approx. 20% w/w (limits 0-50% w/w)
at 30 min.	approx. 80% w/w (limits 25-100% w/w)
at 45 min.	approx. 100 % w/w (limits 50-100% w/w).

13. A pharmaceutical composition according to claim 11 or 12, wherein the calcium-containing compound is selected from the group consisting of bisglycino calcium, calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium citrate malate, calcium cornate, calcium fluoride, calcium glubionate, calcium gluconate, calcium glycerophosphate, calcium hydrogen phosphate, calcium hydroxyapatite, calcium lactate, calcium lactobionate, calcium lactogluconate, calcium phosphate, calcium pidolate, calcium stearate and tricalcium phosphate.

14. A pharmaceutical composition according to any of the preceding claims further comprising a vitamin D (e.g. vitamin D_3).

15. A pharmaceutical composition according to any of the preceding claims comprising a further therapeutically and/or prophylactically active substance that is effective in bone related disorders.

16. A pharmaceutical composition according to any of the preceding claims further comprising an absorption enhancer.

17. A pharmaceutical composition according to any of the preceding claims further comprising a PTH-stabilizing agent.

18. A pharmaceutical composition according to any of the preceding claims in the form of a solid dosage form including tablets, capsules and sachets.

19. A pharmaceutical composition according to any of the preceding claims in the form of a multiple unit dosage form comprising a multiplicity of the same or different pellets or granules.

20. A pharmaceutical composition according to any of the preceding claim comprising one or more of a first type of unit, the first type of unit comprising PTH, and the first type of unit having a layered structure of at least
I) an inner core
ii) a time-controlled layer surrounding the inner core,
iii) a film coating applied on the time-controlled layer, wherein the film coating is substantially water insoluble but permeable to an aqueous medium, and
iv) an outer layer of an enteric coating.

21 (amended). A pharmaceutical composition according to claim 20, wherein the release of the active substance from the unit - when tested *in vitro* as an average of at least three determinations – **within the first two hours** is not more than about 10% w/w at a first pH value below about 4.0, and at a second pH value of from about 5.0 to about 8.0 the active substance is released in such a manner that - after a lag time of from about 0.5 to about 8 hours in which first time period not more than about 10% w/w of the active substance is released - at least about 50% w/w of the active substance contained in the unit is released within a second time period of not more than about 2 hours.

22. A composition according to claim 21, wherein the release of the active substance from the unit– when tested *in vitro* – is not more than about 7.5% w/w such as, e.g., not more than about 5% w/w, not more than about 2.5% w/w or not more than about 1% w/w at the first pH value below about 4.0.

23. A composition according to claim 21, wherein the first pH value is below about 3.5, such as, e.g., below about 3.0, below about 2.5, below about 2.0, below about 1.5 or a pH value corresponding to that of 0.1 N HCl.

24. A composition according to any of claim 20-23, wherein the lag time is from about 1.0 to about 7 hours such as, e.g., from about 1.5 to about 6 hours, from about 2.0 to about 5 hours or from about 2.5 to about 4.5 hours or from about 2.5 to about 4 hours.

25. A composition according to any of claim 20-24, wherein – after said lag time - at least about 60% w/w such as, e.g., at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w or at least 99% w/w of the active substance contained in the unit is released within the second time period of not more than about 2 hours.

26. A composition according to any of claims 21-25, wherein said second time period is not more than about 90 min such as, e.g., not more than about 60 min, not more than about 50 min, not more than about 45 min, not more than about 40 min, not more than about 35 min, not more than about 30 min, not more than about 25 min, not more than about 20 min, not more than about 15 min, not more than about 10 min of not more than about 5 min.

27. A pharmaceutical composition according to any of the preceding claims provided with an enteric coating comprising an enteric polymer that has a pH cut off of at the most about 8.0 such as, e.g. in a range of from about 4.0 to about 7.5, in a range of from about 4.5 to about 7.0, from about 4.9 to about 6.9, from about 5.0 to about 6.5, from about 5.0 to about 6.3, from about 5.0 to about 6.0, from about 5.0 to about 5.9, from about 5.0 to about 5.7, from about 5.0 to about 5.6 or from about 5.0 to about 5.5.

28. A pharmaceutical composition according to any of claims 20-27, wherein the core is selected from pharmaceutically acceptable beads, spheres, granules, granulates, and pellets.

29. A pharmaceutical composition according to claim 28, wherein the lag time is controlled by the time it takes for the swellable layer to swell to such an extent that the film coating layer is disrupted or destructed.

30. A pharmaceutical composition according to any of claims 20-29, wherein the lag time is controlled by the thickness and/or composition of the time-controlled layer.

31. A pharmaceutical composition according to any of claims 20-30, wherein the lag time is further controlled by the thickness and/or composition of the film coating layer.

32. A pharmaceutical composition according to any of claims 20-31, wherein the disruption or destruction of the film coating layer iii) is substantially independent of pH.

33. A pharmaceutical composition according to any of the preceding claims in the form of a multiple unit composition.

34. A pharmaceutical composition according to any of claims 1-32 in the form of a single unit composition.

35. A pharmaceutical composition according to any of the preceding claims comprising i) a PTH, ii) a calcium containing compound, and iii) a vitamin D.

36. A pharmaceutical composition according to any of claims 1-34 comprising i) PTH or a fragment, analog or derivative thereof, and ii) a vitamin D as active substances.

37. A pharmaceutical kit comprising a first and a second component, the first component comprising PTH and the second component comprising a calcium-containing compound, wherein the *in vitro* release of PTH – when tested in a dissolution test of pharmacopoeia standard – is delayed with at least 2 hours and once the release starts, at least 90% w/w such as, e.g., at least 95% or at least 99% of all PTH contained in the composition is released within at the most 2 hours.

38. A pharmaceutical kit according to claim 37, wherein the first component comprising PTH comprises a composition as defined in any of claims 1-36.

39. A pharmaceutical kit according to claim 37 or 38, wherein the two components are contained in the same or different container.

40. A pharmaceutical kit according to any of claims 37-39 further comprising instructions for use of the components.

41. A pharmaceutical kit according to any of claims 37-40 further comprising a third component comprising a second dose of a calcium-containing compound and with instruction for substantially simultaneous oral intake of the first and the second component followed by oral intake of the third component after 2 hours or more such as, e.g., 3 hours or more, 4 hours or more, 5 hours or more, 6 hours or more, 7 hours or more, or 8 hours or more.

42. A pharmaceutical kit according to any of claims 37-41 further comprising a vitamin D.

43. A pharmaceutical kit according to claim 42, wherein vitamin D is included as one of the first or second components or as a separate component.

44. Use of a parathyroid hormone (PTH) in combination with a calcium-containing compound for the manufacture of a medicament for the treatment or prevention of bone-related diseases, wherein

i) an effective amount of a calcium-containing compound is administered to lower the plasma level of endogenous PTH,

ii) an effective amount of PTH is administered to obtain a peak concentration of PTH once the endogeneous PTH level is lowered.

45. Use according to claim 44, wherein the calcium-containing compound and PTH is contained in the same or separate pharmaceutical compositions.

46. Use according to any of claims 44-45, wherein the calcium containing compound is administered orally.

47. Use according to claim 46, wherein PTH is administered at the most 4 hours later than the calcium containing compound.

48. Use according to any of claims 44-47, wherein PTH is administered substantially simultaneous with the calcium containing compound.

49. Use according to any of claims 44-48, wherein PTH and the calcium containing compound is contained in a composition as defined in any of claims 1-36 or a kit as defined in any of claims 37-43.

50. A method for administering active substances to the small intestine or colon, the method comprises administering to a patient a sufficient amount of a pharmaceutical composition defined in any of claims 1-36, a kit as defined in any of claims 37-43 or a medicament as defined in any of claims 44-49.

51. A method for treatment or prevention of a bone related disorder including osteoporosis, the method comprising oral administration to a patient in need thereof a sufficient amount of PTH in a pharmaceutical composition as defined in any of claims 1-36, a kit as defined in any of claims 37-43 or a medicament as defined in any of claims 44-49.